Statistical Evaluation and Review

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Product/Application:	Recombinant urate oxidase enzyme (SR29142)
Indication:	Treatment and prophylaxis of hyperuricemia in patients with leukemia and lymphoma.
Sponsor:	Sanofi-Synthelabo Inc.
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From:	Ghanshyam Gupta, Ph.D., HFM-219 Ghanshyam Gupta 11-30-00
Through:	P. A. Lachenbruch, Director, Division of Biostatistics, HFM-215
To:	David Maybee, M. D., HFM-573
	Sharon Sickafuse, HFM-588
	Chron,
	DCC
	S Ellenberg, HFM-210

Background:

Patients treated for non-Hodgkins lymphoma, acute lymphoblastic leukemia,or some solid tumor cancers, with high tumor burden and high sensitivity to chemotherapy, tend to show the highest uric acid levels and are most at risk of hyperuricemia and its complications such as renal insufficiency. The current therapies are allopurinol and alkaline hydration. SR29142 is a recombinant urate oxidase enzyme, a highly potent and fast acting uricolytic agent.

The application for the approval of SR29142 is based on one phase I study, two phase II studies, one phase III study, and one long-term safety study. This report will briefly review the phase I and II studies. Most of the review will be based on the pivotal phase III study in 52 patients.

Phase I study (TDR2681):

This was a tolerability and pharmacokinetic open-label, non-randomized study of single (0.05 to 0.20 mg/kg) and multiple (0.10 to 0.20 mg/kg) doses of SR29142 in 28 healthy male subjects. Plasma concentration (AUC) and maximum plasma concentration were dose dependent. The mean terminal half life was estimated to be 18.0 hours. The multiple dose regimen indicated that the steady state had been reached by Day 5.

Phase II Study (ACT2511, ACT2694):

These were both open-label, multi-center, repeated dose study with a dose validation phase followed by an accrual phase. In study ACT2511, a total of 107 patients were enrolled including 20 in the dose validation phase. The initial dose of 0.15 mg/kg could be increased to 0.20 mg/kg, 0.25 mg/kg, or higher as needed in an ascending-dose scheme. The dose that successfully controlled or prevented hyperuricemia in the validation phase was to be selected for the accrual phase. In study ACT 2511, 0.15 mg/kg was selected the dose for the accrual phase. In the second phase II study, ACT2694, a total of 131 patients were enrolled with 12 patients on 0.15 mg/kg and 22 patients on 0.20 mg/kg during the validation phase. The accrual phase of the study maintained the dose of 0.20 mg/kg.

A response rate of 99.0% and 95.0% was observed in study ACT2511 and ACT2694 respectively. Uric acid levels, 4-hours post first dose of SR29142, were reduced by 88 ± 12% in ACT2511 and 84.9 ± 12.6% in ACT 2694, and remained reduced throughout the study dosing period and thereafter.

Phase III study (EFC2975):

This was an open-label, randomized, multi-center, repeated dose comparison study of SR29142 with allopurinol. The patients were stratified according to uric acid levels at presentation (<8.0 mg/dL and >=8.0 mg/dL) and disease (leukemia and lymphoma). The study randomized a total of 52 patients, 27 patients to SR29142 and 25 patients to the

allopurinol. Patients received 0.20 mg/kg SR29142, infused once daily for 30 minutes, or allopurinol daily oral doses according to standard medical practice, for five to seven days.

The primary efficacy endpoint was the area under the curve of the serial plasma uric acid levels from start of study drug administration until 96 hours from treatment start (AUC96). The secondary endpoints were the percentage of reduction in plasma uric acid at four hours after the first of study drug, plasma uric acid levels at each time point, and duration of therapy (hours) until control of uric acid values. In addition, subset analyses of the primary endpoint within each stratum was also planned.

Study EFC2975 Results

Baseline Comparisons:

The study enrolled 52 patients, 25 patients to allopurinol group and 27 patients to the SR29142 group. There were 34 (65%) male patients. The distribution of patients between the two groups by sex was not significantly different (p=0.33). Majority of patients was of Caucasian origin (65%). Most of the patients (86.5%) belonged to the ECOG category of 0 or 1. There was no difference between the two groups with regard to age or weight. The same was true of the hyperuricemic status of patients at baseline. There were 19 (36.5%) patients with hyperuricemic status. Baseline uric acid was also not significantly different between the two groups. Similar results were found for the baseline uric acid levels when analyzed by sex. Overall, the two groups were found to be comparable at the baseline.

Table 1. Baseline Comparisons

Baseline Variable	TREATMENT		p-value
	Allopurinol (n=25)	SR29142 (n=27)	
Sex:			0.33
Male	18 (72.0%)	16 (59.26%)	
Female	7 (28.0%)	11 (40.74%)	
Race:			0.36
Caucasian	18 (72.0%)	16 (59.26%)	
Hispanic/Asian	5 (20.0%)	5 (18.52%)	
Other	2 (8.0%0	6 (22.22%)	
ECOG Category			0.12
0	18 (72.0%)	14 (51.85%)	
1	30(12.0%)	10 (37.04%)	
2	0 (0.0%)	1 (3.70%)	
3	4 (16.0%)	2 (7.41%)	
Age (years): All	7.82 ± 1.00	7.09 ± 0.91	0.59
Male	8.03 ± 1.28	6.89 ± 1.07	0.51
Female	7.29 ± 1.54	7.36 ± 1.65	0.97
Weight (kg): All	35.8 ± 4.78	32.6 ± 4.43	0.63
Male	37.2 ± 5.90	31.7 ± 5.43	0.50
Female	32.2 ± 8.35	33.9 ± 7.79	0.89
Baseline Uric Acid	7.16 ± 3.35	7.91 ± 3.42	0.43
Male	6.82 ± 0.83	8.10 ± 0.81	0.28
Female	8.04 ± 1.07	7.64 ± 1.15	0.81
Hyperuricemic Status:			0.94
NO	16 (64.0%)	17 (63.0%)	
YES	9 (36.0%)	10 (37.0%)	
Disease Diagnosis:*			0.87
Leukemia	19 (76.0%)	20 (74.0%)	
Lymphoma	6 (24.0%)	7 (26.0%)	

*Two patients (0010008, 003001) could be classified in both groups. Both patients are Classified as Leukemia patients in this tabulation.

Efficacy Results:

The primary endpoint of the study was area under the curve from 0 to 96 hours after the treatment. The two treatment groups were found to be highly significantly different. Within each gender, the results of the primary endpoint were again highly significant with male patients smaller AUC in the allopurinol group while female patients smaller AUC in the SR29142 group. The interaction between sex and treatment was close to significant ($p=0.0515$). The interaction between hyperuricemic status and treatment was also found to be significant ($p=0.0167$). Within each hyperuricemic status, the two treatment groups remained highly significantly different with regard to the primary endpoint of AUC. The AUC was also analyzed by disease status. Two of the patients could be classified either of the Leukemia or Lymphoma groups. With the both patients considered in the Leukemia group, within each disease class, the two treatment groups were highly significantly different. The results remained the same if the two patients were considered in the Lymphoma group. There was no interaction between treatment and disease status ($p=0.15$).

We also analyzed by age group. Within each of the three age groups, AUC was significantly different between the two treatment groups with a large reduction in AUC for the SR29142 group. No particular trend in AUC values for the age groups were noticed. Analysis by race also showed the similar results. There were only three patients of African origin. Therefore, no formal comparison is provided for this group. The other category includes patients from Hispanic and Asian origin.

Table 2. Analysis of AUC (0-96 Hrs)

AUC (0-96 HRS)	TREATMENT (Mean ± SE)		P-VALUE
	ALLOPURINOL N=25	SR29142 N=27	
ALL PATIENTS	328.5 ± 25.85	128.09 ± 13.53	<0.0001
SEX:			
MALE	306.9 ± 29.59 N=18	145.2 ± 20.95 N=16	<0.0001
FEMALE	384.2 ± 49.49 N=7	103.2 ± 10.30 N=11	<0.0001
HYPERURIC STATUS:			
YES	440.0 ± 40.37 N=9	162.4 ± 27.43 N=10	<0.0001
NO	265.9 ± 21.31 N=16	107.9 ± 12.44 N=17	<0.0001
DIS DIAGNOSIS*			
Leukemia	361.7 ± 29.55 n=19	140.5 ± 16.75 n=20	<0.0001
Lymphoma	223.6 ± 22.61 n=6	92.5 ± 15.33 n=7	0.0005
RACE			
Caucasian	303.0 ± 23.77 n=18	146.5 ± 20.84 n=16	<0.0001
Black	216.4 n=1	65.8 ± 2.48 n=2	----------
Other	423.8 ± 70.58 n=6	109.2 ± 10.47 n=9	0.0001
AGE GROUP			
< 5 yrs	303.5 ± 32.02 N=10	129.5 ± 23.51 N=11	0.0003
6 – 12 yrs	379.3 ± 49.04 N=9	134.0 ± 19.03 N=11	<0.0001
> 13 yrs	294.0 ± 57.41 N=6	111.8 ± 36.15 N=5	0.0310

*The two patients who could belong to any of the disease status are considered to belong to Leukemia group. If they are considered to belong to Lymphoma group, the difference still remains highly significant between the two groups with significance values of $p<0.0001$ for Leukemia and $p=0.0066$ for Lymphoma patients.

Primary Endpoint by Center

Although there was a clear treatment difference between the two treatment group, it was of interest to examine if the effect was consistent within each center. Due to insufficient number of patients per center, center by treatment interaction was not analyzed. Instead means and standard errors of area under the curve (AUC0_96) by center are provided in the table below.

Table 3. Means and Standard Errors of $AUC_{0\text{-}96}$ by center.

CENTER	ALLOPURINOL			SR29142		
	N	MEAN	SE	N	MEAN	SE
001	5	376.27	87.92	9	116.97	14.79
003				2	206.56	135.26
004	3	267.55	43.53	3	103.95	25.15
005	5	358.89	50.94	6	101.79	12.60
007	3	297.96	57.18	3	116.09	34.18
010	9	315.69	42.82	4	180.40	49.91

The center number 3 did not enter any patient in the control group. The two patients from this center belonged to SR29142 group and had the largest mean area under the curve. Overall, the area under the curve was lower in the SR29142 group in all the centers.

Secondary Endpoints:

The secondary endpoints were the percentage of reduction in plasma uric acid at four hours after the first of study drug, plasma uric acid levels at each time point, and duration of therapy (hours) until control of uric acid values. Reduction in plasma uric acid at four hours after the administration of treatment was 0.72 and 6.21 for the allopurinol and SR29142 groups, respectively. The variances of the two treatment groups were found to be significantly different (Bartlett test: $p<0.0001$). Taking into account the unequal group variances, the comparison of the two groups is based on the Welch test. Percent reduction in plasma uric acid at 4 hours was also analyzed. The median reduction was 10% and 89% for allopurinol and SR29142 groups respectively (Wilcoxon Rank Sum Test: $p<0.0001$). Duration of treatment was significantly smaller by about half a day in the SR29142 group.

Table 4. Secondary Endpoints by Treatment.

SECONDARY ENDPOINT	TREATMENT		P-VALUE
	ALLOPURINOL	SR29142	
Reduction in Plasma Uric Acid at 4 hours (mg/dl)	N=25 -0.72 ± 0.15	N=27 -6.21 ± 0.49	<0.0001+
Percent reduction in Plasma Uric Acid at 4 hours (Median, and range)	-10.3 (-63.6, 4.9)	-89.2 (-97.8, -69.6)	<0.0001++
Duration of Therapy (days) until UA levels controlled	N=25 5.32 ± 0.20	N=27 4.78 ± 0.16	0.0382+++

+ Welch Test.

++ Wilcoxon Rank Sum test.

+++ Student's t-test.

Adverse Experience

In the table below, we provide proportion of adverse experience (> 0.04) by treatment in a descending order of occurrence in the SR29142 group. Vomiting occurred most in both the treatment groups with slightly higher proportion in the SR29142 group (p=0.26). Occurrence of fever and nausea followed vomiting.

PROPORTION OF ADVERSE EXPERIENCE BY TREATMENT

Adverse Experience	Allopurinol (N=25)	SR29142 (N=27)
VOMITING	0.4	0.56
FEVER	0.32	0.41
NAUSEA	0.24	0.33
BACK PAIN	0.32	0.30
DIARRHEA	0.16	0.30
ABDOMINAL PAIN	0.4	0.26
PAIN	0.32	0.26
HEADACHE	0.12	0.26
RESPIRATORY DISORDER	0.24	0.22
FLUID OVERLOAD	0	0.22
NERVOUSNESS	0.2	0.19
CONSTIPATION	0.16	0.19
HYPOCALCAEMIA	0.16	0.19
SKELETAL PAIN	0.12	0.19
HAEMATURIA	0.08	0.19
BRADYCARDIA	0.16	0.15
RASH	0.04	0.15
MUCOSITIS NOS	0.32	0.11
ANOREXIA	0.24	0.11
EPISTAXIS	0.24	0.11
COUGHING	0.16	0.11
HYPOKALAEMIA	0.16	0.11
ANAEMIA	0.12	0.11
HYPERTENSION	0.08	0.11
HYPOTENSION	0.08	0.11
HYPOXIA	0.08	0.11
OEDEMA	0.08	0.11
OEDEMA PERIORBITAL	0.08	0.11

PROPORTION OF ADVERSE EXPERIENCE BY TREATMENT

Adverse Experience	Allopurinol	SR29142
PURPURA	0.08	0.11
DIZZINESS	0.04	0.11
HAEMATOMA	0.04	0.11
OLIGURIA	0.04	0.11
PLEURAL EFFUSION	0.04	0.11
INJECTION SITE PAIN	0.2	0.07
COAGULATION DISORDER	0.16	0.07
ANXIETY	0.12	0.07
DYSPNOEA	0.12	0.07
HYPERGLYCAEMIA	0.12	0.07
THROMBOCYTOPENIA	0.12	0.07
WEIGHT DECREASE	0.12	0.07
INJECTION SITE REACTION	0.08	0.07
MONILIASIS	0.08	0.07
PHARYNGITIS	0.08	0.07
ARTHRALGIA	0.04	0.07
FLATULENCE	0.04	0.07
INJECTION SITE BLEEDING	0.04	0.07
PERICARDIAL EFFUSION	0.04	0.07
SKIN DRY	0.04	0.07
SURGICAL SITE REACTION	0.04	0.07
TACHYCARDIA	0.04	0.07
HERPES SIMPLEX	0	0.07
HYPONATRAEMIA	0	0.07
AGITATION	0.12	0.04
GRANULOCYTOPENIA	0.12	0.04
HEART VALVE DISORDERS	0.12	0.04
TUMOUR LYSIS SYNDROME	0.12	0.04
ARRHYTHMIA	0.08	0.04
FLUSHING	0.08	0.04
GLYCOSURIA	0.08	0.04
HEPATOMEGALY	0.08	0.04
INFECTION	0.08	0.04
OEDEMA GENERALISED	0.08	0.04
SEPSIS	0.08	0.04
ARTHROSIS	0.04	0.04

Conclusions:

The pivotal phase III study (EFC2975) demonstrates that the patient population in the two treatment groups were comparable. The difference between the two treatment groups was highly significant with regard to the primary endpoint of AUC_{0-96} as well as the secondary endpoints of reduction in plasma uric acid at 4 hours and percent reductions in plasma uric acid at 4 hours. The difference in the AUC in favor of the SR29142 treatment remained significant in all the subgroups analyzed. AUC remained lower for the SR29142 group within each of the centers. Center number 2 did not have any patients in ALLPURINOL group.

In the pivotal study, four patients did not complete the study. One of the four patients dropped out of the study due to an adverse event belonged to SR29142 group. The remaining three patients belonged to Allopurinol group. Two of these patients died. One patient dropped out due to some other reasons.

The most frequently occurring adverse experiences in both groups were vomiting, fever, and nausea. Fluid overload occurred only in the SR29142 group.